IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of	**MAIL STOP AF**
Ignacio Blanco Blanco	Group Art Unit: 1652
Application No.: 10/549,759	Examiner: ROSANNE KOSSON
Filed: September 19, 2005	Confirmation No.: 6945
For: USE OF ALPHA-1 ANTITRYPSIN FOR THE PREPARATION OF MEDICAMENTS FOR THE TREATMENT OF FIBROMYALGIA	

DECLARATION OF IGNACIO BLANCO BLANCO UNDER § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Ignacio Blanco Blanco, hereby declare as follows:

1. I am a citizen of Spain, and reside at Oviedo, Spain.

2. My education and professional history are outlined in my attached curriculum vitae (Attachment A).

3. I am the sole inventor in the referenced application, and submit this Declaration in support thereof.

4. Attached hereto are print-outs dated March 22, 2007 from the Alpha One International Registry (AIR) (see Attachment B). (The attached print-outs are from the Spanish AATD Registry, which is a corresponding national registry of the AIR. The AIR International Registry is not accessible as doctor users have access only to their corresponding national registry.)

5. The printed information discloses the information in the Registry relating to the two patients referred to in the cited Blanco reference (two sisters, designated here as patients 205 and 206). The Registry information relating to those

two patients is confidential information that is not publicly available, even to those with general access to the Registry. Rather, it is accessible only by the registering doctor. Specifically, the information is available only to the doctor who has registered the particular patients, and the Registry requires that the doctor provide a confidential user name and access code (or key code). The confidential listings are available only to the accessing doctor, and only when such confidential and personal information has been entered.

6. As can be seen in attachment C, the Registry information made available to Dr. Blanco, even after entering his confidential user name and key code, includes only that corresponding to his nine patients. The information pertaining to those patients includes the following: registry number, release date, patient initials, date of birth, sex, pulmonary function (F_{ev1} Post (Basal)), FVC Post Basal, substitutive treatment (yes or no), and whether monitoring is performed.

7. The accessing doctor may consult the data of his/her patients by clicking the Registry number and accessing a new page containing demographic and clinical data. See Attachments D & E (files with the data of the two sister patients with alpha-1 antitrypsin deficiency, patient numbers 205 and 206, in Spanish with translations attached).

8. The Registries record only the data appearing in the presented database fields. Thus, in Dr. Blanco's patients, the only data having been reported are those shown in the database. Any additional information, e.g., that regarding the effect of substitutive treatment for AAT Deficiency or use of AAT for other conditions such as fibromyalgia, has never been reported and thus is not accessible from the Registry. The information presented within the Registry relates only to the treatment

of congenital AAT deficiency. There is no field for the entry of information relating to other maladies such as fibromyalgia, and no such information has been introduced. Accordingly, there is nothing within the Registry - whether public or private - that relates to the incidence or possible treatment of fibromyalgia in those patients.

9. Although it has been stated that the patients have received substitutive treatment, the nature of that treatment and its results were never entered into the Registry, nor was that information publicly available.

10. Also attached hereto is a publication entitled "Ongoing Research in Europe: Alpha One International Registry (AIR) Objectives and Development", *Eur Respir J* (2007) 29:582-586 (Attachment F). This reference discusses generally the development and objectives of the Alpha One International Registry in response to the recommendation of the World Health Organization. The reference describes the protocol of handling of information, emphasizes confidentiality of that information and patient characteristics, and focuses primarily on the geographic distribution of the various forms of Alpha One Trypsin Deficiency. As stated in the reference, the information provided is carefully controlled. Additionally, there is no mention of the disclosure of substitutive treatment, nor is there any suggestion that the use of substitutive treatment for other, unrelated conditions, is even entered into the system or publicly accessible. This confirms that information such as is relied upon in the referenced application was not included in the AIR registry, and was not publicly available.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false

statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

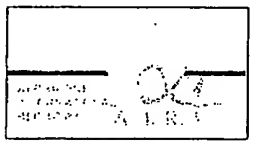
Date: _____ By: _____
Ignacio Blanco Blanco

ATTACHMENT A

CURRICULUM VITAE

(to follow)

ATTACHMENT B



REGISTRO ESPAÑOL DE PACIENTES CON DEFICIT DE ALFA-1 ANTITRIPSINA

ACCESO AL REGISTRO
Usuario
Clave
Solicitar claves | Entrar ->

El desarrollo de esta aplicación ha sido posible gracias a la colaboración de **Q.F BAYER**, una beca del área de **IRTS** de la **SEPAR** y una beca (FIS:02/10003) del **Fondo de Investigaciones Sanitarias (FISS)**.

FUNDACIÓN DEL REGISTRO ESPAÑOL DEL DAAT

Debido a la escasa prevalencia del DAAT, surgió la necesidad de acumular información derivada del estudio de grupos de pacientes con esta enfermedad. El Registro Español de pacientes con DAAT se fundó el 13.04.1993, pero debido al pequeño número de pacientes que se esperaba reclutar, no nació con el objetivo de ser una alternativa a los ensayos clínicos para conocer la eficacia del tratamiento, sino que el propósito inicial del Registro fue:

OBJETIVOS DEL REGISTRO

1. Conocer las características y la frecuencia del DAAT en España.
2. Establecer normativas adaptadas a nuestro país sobre el tratamiento y seguimiento de pacientes con el déficit.
3. Ofrecer información a los médicos que traten a estos pacientes en toda España.
4. Incrementar el conocimiento y el interés por esta "no tan rara" enfermedad e intentar disminuir el infradiagnóstico o el retraso en el conocimiento del DAAT.
5. Recoger información acerca de la evolución funcional, la frecuencia del tratamiento sustitutivo y la posible aparición de efectos adversos con este tratamiento.
6. Ofrecer soporte técnico para la determinación del fenotipo Pi y si es necesario del genotipo en aquellos individuos con sospecha de DAAT.

ORGANIZACIÓN DEL REGISTRO

Desde su origen, el Registro es un grupo de trabajo del Área IRTS (Insuficiencia Respiratoria y Trastornos de Sueño) de la SEPAR (Sociedad Española de Neumología y Cirugía Torácica). Lo componen dos coordinadores, un Comité Asesor y 64 centros participantes distribuidos por toda España y Andorra

La base de datos se encuentra en el centro coordinador, en el que también existe el laboratorio central que ofrece la posibilidad de determinar el fenotipo Pi y en casos especiales el genotipo mediante secuenciación del DNA.

El Comité Asesor se reúne periódicamente para evaluar y analizar la evolución de la base de datos del Registro y actualizar las normativas referentes al tratamiento sustitutivo con AAT y el seguimiento de los pacientes.

Coordinadores:

Marc Miravitlles . Servicio de Neumología, Hospital Clínic i Provincial de Barcelona.

Rafael Vidal. Servicio de Neumología, Hospital General Vall d'Hebron. Barcelona

Comité asesor:

Juan Carlos Barros-Tizón. Vigo

Ignacio Blanco. Langreo

Ana Bustamante. Torrelavega

Francisco Casas. Granada

Carlos Escudero. Oviedo

Pedro P. España. Galdakao

Maite Martínez. Madrid

Gestión del registro español

Beatriz Lara. Barcelona

Laboratorio central del registro

Rosendo Jardí y Francisco Rodríguez-Frías. Servicio de Bioquímica, Hospital General Vall d'Hebron.

SPANISH REGISTRY OF PATIENTS WITH ALFA-1 ANTITRYPSIN DEFICIENCY

REGISTRY ACCESS	
User Key	
Asking for key	Log in

FOUNDING OF THE SPANISH REGISTRY OF AATD

Owing to the scarce prevalence of AATD, the necessity arose to accumulate information derived from studying groups of patients with this condition. The Spanish Registry of patients with AATD was founded on 13.04.1993, however, owing to the small number of patients that were to be recruited, it was not set up with the objective of being an alternative to clinical trials in order to discover the effectiveness of the treatment. Instead, the initial aim of the Registry was:

OBJECTIVES OF THE REGISTRY

1. To discover the characteristics and frequency of AATD in Spain.

2. To establish rules adapted to our country on the treatment and follow-up of patients with this deficit.

3. To offer information to doctors who treat these patients in Spain.

4. To widen the knowledge and interest in this condition (which is not so rare) and try to reduce the infradiagnosis of or delays in recognising AATD.

5. To collect information on the functional evolution, the frequency of alternative treatments or the possible appearance of side affects with this treatment.

6. To offer technical support for determining the Pi phenotype and if necessary the genotype of those individuals suspected of having AATD.

ORGANISATION OF THE REGISTRY

From the outset, the Registry is a working group in the IRTS (Insufficient Respiratory and Sleep Disorder) Area of SEPAR (Spanish Society of Pneumology and Thoracic Surgery). It comprises of two coordinators, an Advisory Committee and 64 participating centres distributed through Spain and Andorra.

The database can be found in the coordinating centre, where the central laboratory is also located, which offers the possibility of determining the Pi phenotype and, in special cases, the genotype by means of DNA sequencing.

The Advisory Committee meets regularly in order to evaluate and analyse the evolution of the Registry's database and update the rules in reference to alternative treatment with AAT and patient follow-up.

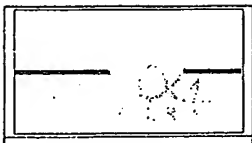
Coordinators:

Advisory Committee:

Management of the Spanish registry:

Registry's Central Laboratory:

ATTACHMENT C



REGISTRO ESPAÑOL DE PACIENTES CON DEFICIT DE ALFA-1 ANTITRIPSINA

- REGISTRO DE PACIENTES
  - Registrar nuevo paciente
  - Listado de pacientes
- Situación actual del Registro
- Estudios en fase de realización o desarrollo
- Publicaciones
- Preguntas abiertas
- Prolastina
- Trypsone
- Envios de muestra

SALIR DEL REGISTRO >>

Pendiente: Faltan datos de seguimiento semestral. Por favor, cumplimente los datos del formulario de seguimiento del paciente.

Nº registro	Fecha alta	Iniciales	Nacimiento	Sexo	Fev1 Post (Basal)	FVC Post (Basal)	Tratamiento sustitutivo	Perdido	Exitus	Seguimientos
205	04/02/2002	EAF	12/06/1951	Mujer	2,00	2,36	Si			Pendiente
206	04/02/2002	RAF	12/04/1947	Mujer	1,40	2,30	Si			Pendiente
207	04/02/2002	CFG	14/06/1935	Mujer	1,80	2,20				Pendiente
215	05/02/2002	AAG	01/01/1941	Hombre	2,60	4,10				Pendiente
216	05/02/2002	HFG	24/08/1940	Mujer	2,40	2,80			Si	
217	05/02/2002	JCGC	22/12/1940	Hombre	0,80	2,50	Si			Pendiente
218	05/02/2002	EFF	24/07/1928	Mujer	1,60	2,50			Si	
219	05/02/2002	MDVT	15/05/1954	Hombre	1,50	2,30	Si		Si	
665	13/04/2004	MAMD	24/03/1962	Hombre	1,35	2,40				Pendiente

SPANISH REGISTRY OF PATIENTS
WITH ALFA-1 ANTITRYPSIN DEFICIENCY

Registration No.	Release date	Initials	Date of birth	Sex	Fev1 Post (Basal)	FVC Post (Basal)	Alternative treatment	Lost	Exitus	Follow-up
205										
206										
207										

ATTACHMENT D

REGISTRO ESPAÑOL DE PACIENTES CON DEFICIT DE ALFA-1 ANTITRIPSINA

- REGISTRO DE PACIENTES
  - Registrar nuevo paciente
  - Listado de pacientes
- Situación actual del Registro
- Estudios en fase de realización o desarrollo
- Publicaciones
- Preguntas abiertas
- Prolastina
- Trypsone
- Envios de muestra

SALIR DEL REGISTRO >>

MODIFICAR DATOS DE PACIENTE

Ver seguimientos >

Nuevo seguimiento >

Por favor, siga las siguientes reglas para la introducción de datos:

Utilice el signo **PUNTO** para indicar **decimales**: (Ej.: 34.203)

Indique las **fechas** siempre con el **formato dd/mm/aaaa**: (Ej: 23/02/2001)

PACIENTE Nº: 205

INICIALES PACIENTE: EAF

Código de país: E **Fecha de inclusión:** 04/02/2002

DEMOGRAFÍA

Fecha de nacimiento: 12/06/1951 dd/mm/aaaa

Sexo: Fermale

Altura: 148 Unidades de altura: Cm

Peso (kg): 58 kilos

TABAQUISMO

Fumó alguna vez? No

Edad de inicio: años

Dejó de fumar?

Edad en que dejó de fumar años

Consumo medio de cigarrillos diarios:

Consumo medio de cigarros diarios:

Pipa - g/semana:

MOTIVO DE LA DETERMINACIÓN DE AAT

Motivo para determinación de AAT: Family screening

Fenotipo: Z

Otro fenotipo deficiente:

Fecha del diagnóstico del déficit AAT: 15/01/1994 dd/mm/aaaa

HISTORIA CLÍNICA

Enfermedad pulmonar : Yes

Bronquitis crónica : No

Enfisema: Yes

Asma: Yes

Bronquiectasias: Yes

Otra enfermedad pulmonar ? No

Especificar:

Edad al inicio de los síntomas respiratorios

Años: 40 Meses:

Síntoma principal Dyspnoea on exertion

OTROS DIAGNÓSTICOS No

Diagnóstico 1: fibromialgia reumática

ICD código diagnóstico 1: Ver Tabla de códigos ICD versión:

Diagnóstico 2:

ICD código diagnóstico 2: Ver Tabla de códigos ICD versión:

Diagnóstico 3:

ICD código diagnóstico 3: Ver Tabla de códigos ICD versión:

Trasplante de pulmón:

Fecha del trasplante de pulmón: dd/mm/aaaa

Reducción de volumen pulmonar:

Fecha de reducción de volumen pulmonar: dd/mm/aaaa

Trasplante de hígado:

Fecha del trasplante de hígado: dd/mm/aaaa

Ha sufrido neumonías?

En caso afirmativo, ¿Cuántas veces?:

Número desconocido

DATOS TC

TC del tórax : No

Fecha del TC de tórax: 12/05/1994 dd/mm/aaaa

TRATAMIENTO ACTUAL

Medicación para la enfermedad pulmonar: Yes

Oxigenoterapia domiciliaria: No

TRATAMIENTO SUSTITUTIVO

Alguna vez ha recibido tratamiento sustitutivo? Yes

Fecha de inicio : 10/07/1995 dd/mm/aaaa

Dejó el tratamiento? No

Fecha de interrupción: dd/mm/aaaa

FUNCIONALISMO PULMONAR

Fecha de las primeras pruebas disponibles: 10/07/1994 dd/mm/aaaa

FEV1 pre-broncodilatador (L): 2 litros

FEV1 post-broncodilatador (L): 2 litros

FVC pre-broncodilatador (L): 2,36 litros

FVC post-broncodilatador (L): 2,36 litros

VC lenta pre-broncodilatador (L): 2,37 litros

VC lenta post-broncodilatador (L): 2,37 litros

Fecha de las pruebas más recientes 10/12/2001 dd/mm/aaaa

FEV1 pre-broncodilatador (L): 1,9

FEV1 post-broncodilatador : 1,9 litros

FVC pre-broncodilatador (L): 2

FVC post-broncodilatador : 2 litros

VC lenta pre-broncodilatador (L): 2 litros

VC lenta post-broncodilatador : 2 litros

KCO (%): %

ENZIMAS HEPÁTICAS

Enzimas hepáticas : Yes

Fecha de determinación: 06/06/1999 dd/mm/aaaa

ALAT/SGOT Elevada:	No
ASAT/SGPT Elevada:	No
GGT Elevada:	No
FA Elevada:	No

DATOS CUESTIONARIO ST GEORGE

Puntuación total SGRQ:	

HISTORIA LABORAL

Trabaja actualmente:	No	Si **NO**, especifique el motivo:	Other
Muestra de plasma?	Yes		
Muestra de sangre total?	Yes		

FECHA FINAL

Fecha de fallecimiento :	dd/mm/aaaa
Causa de muerte :	
Otra causa, especificar:	
Se realizó autopsia:	

Modificar Paciente - Cancelar

Patient N°: 205

PATIENT'S INITIALS: EAF

Country code: E Inclusion date: 04/02/2002

DEMOGRAPHICS

Date of birth:		Sex:	
12/06/1951 dd/mm/yyyy		Female	
Height	Height units	Weight (kg):	
148	Cm	58	kilos

SMOKING HABITS

Have you ever smoked?	No	Age started:	years old
Have you given up smoking?		Age stopped:	years old

Average daily consumption of cigarettes:

Average daily consumption of cigars:

Pipe - g/week:

REASON FOR DETERMINING AAT

Reason for determining AAT: Family screening

Phenotype: Z

Other deficient phenotype:

Date of diagnosis of AAT deficit: 15/01/1994 dd/mm/yyyy

CLINICAL HISTORY

Lung disease	Yes		
Chronic bronchitis	No		
Emphysema	Yes		
Asthma	Yes		
Bronchiectasis	Yes		
Other lung disease	No	Specify	

Age respiratory symptoms started		Years old 40	Months
Principal symptom	Dyspnoea on exertion		

Other diagnosis	No		
Diagnosis 1: rheumatic fibromyalgia			
ICD code			
Diagnosis 1	See Code Table	ICD version	
Diagnosis 2			
ICD Code			
Diagnosis 2	See Code Table	ICD version	
Diagnosis 3			
ICD Code			
Diagnosis 3	See Code Table	ICD version	
Lung transplant		Date of lung transplant:	dd/mm/yyyy
Reduction in lung volume		Date of reduction of lung volume:	dd/mm/yyyy
Liver transplant:		Date of liver transplant:	dd/mm/yyyy
Have you suffered from pneumonia?			
If so, how many times?		Unknown number	
TC data			
Thorax TC:	No	Date of Thorax TC:	12/05/1994 dd/mm/yyyy
CURRENT TREATMENT			
Medication for lung disease	Yes	Home oxygen therapy:	No
ALTERNATIVE TREATMENT			
Have you received an alternative treatment	Yes	Start date:	10/07/1995 dd/mm/yyyy
Did you stop treatment?	No	Interruption date	dd/mm/yyyy
PULMONARY FUNCTIONING			
Date of first tests available	10/07/1994	dd/mm/yyyy	
FEV1 pre-bronchodilator (L):	2 litres	FEV1 post-bronchodilator (L)	2 litres
FVC pre-bronchodilator (L):	2.36 litres	FVC post-bronchodilator (L)	2.36 litres
Slow VC pre-bronchodilator (L):	2.37 litres	Slow VC post-bronchodilator (L)	2.37 litres
Date of most recent tests	10/12/2001	dd/mm/yyyy	
FEV1 pre-bronchodilator (L):	1.9 litres	FEV1 post-bronchodilator (L)	1.9 litres
FVC pre-bronchodilator (L):	2 litres	FVC post-bronchodilator (L)	2 litres
Slow VC pre-bronchodilator (L):	2 litres	Slow VC post-bronchodilator (L)	2 litres
KCO (%):	%		
HEPATIC ENZYMES			
Hepatic enzymes: Yes		Date of determination: 06/06/1999 dd/mm/yyyy	

High ALAT/SGOT	No
High ASAT/SGPT	No
High GGT	No
High FA	No

ST GEORGE QUESTIONNAIRE DATA

Total score SGRQ:

WORK HISTORY

Do you currently work:	No	If not, specify the reason	Other
Plasma sample	Yes		
Total blood sample	Yes		

END DATE

Date of death: dd/mm/yyyy

Cause of death:

Other cause, specify:

Was an autopsy carried out:

ATTACHMENT E

REGISTRO ESPAÑOL DE PACIENTES CON DEFICIT DE ALFA-1 ANTITRIPSINA

- REGISTRO DE PACIENTES
  - Registrar nuevo paciente
  - Listado de pacientes
- Situación actual del Registro
- Estudios en fase de realización o desarrollo
- Publicaciones
- Preguntas abiertas
- Prolastina
- Trypsone
- Envios de muestra

SALIR DEL REGISTRO >>

MODIFICAR DATOS DE PACIENTE

Ver seguimientos

Nuevo seguimiento

Por favor, siga las siguientes reglas para la introducción de datos:

- Utilice el signo **PUNTO** para indicar **decimales**: (Ej.: 34.203)

  Indique las **fechas** siempre con el **formato dd/mm/aaaa**: (Ej: 23/02/2001)

PACIENTE Nº: 206

INICIALES PACIENTE: RAF

Código de país: E **Fecha de inclusión:** 04/02/2002

DEMOGRAFÍA

Fecha de nacimiento: 12/04/1947 dd/mm/aaaa

Sexo: Fermale

Altura: 149 Unidades de altura: Cm

Peso (kg): 57 kilos

TABAQUISMO

Fumó alguna vez? No

Edad de inicio: años

Dejó de fumar?

Edad en que dejó de fumar años

Consumo medio de cigarrillos diarios:

Consumo medio de cigarros diarios:

Pipa - g/semana:

MOTIVO DE LA DETERMINACIÓN DE AAT

Motivo para determinación de AAT: Family screening

Fenotipo: Z

Otro fenotipo deficiente:

Fecha del diagnóstico del déficit AAT: 18/07/1984 dd/mm/aaaa

HISTORIA CLÍNICA

Enfermedad pulmonar : Yes

Bronquitis crónica : Yes

Enfisema: Yes

Asma: Yes

Bronquiectasias: Yes

Otra enfermedad pulmonar ? No

Especificar:

Edad al inicio de los síntomas respiratorios

Años: 35 Meses:

Síntoma principal Attacks of dyspnoea

OTROS DIAGNÓSTICOS Yes

Diagnóstico 1:	fibromialgia reumática		
ICD código diagnóstico 1:	Ver Tabla de códigos	ICD versión:	
Diagnóstico 2:			
ICD código diagnóstico 2:	Ver Tabla de códigos	ICD versión:	
Diagnóstico 3:			
ICD código diagnóstico 3:	Ver Tabla de códigos	ICD versión:	

Trasplante de pulmón:	No	Fecha del trasplante de pulmón:	dd/mm/aaaa
Reducción de volumen pulmonar:	No	Fecha de reducción de volumen pulmonar:	dd/mm/aaaa
Trasplante de hígado:	No	Fecha del trasplante de hígado:	dd/mm/aaaa
Ha sufrido neumonías?	No		
En caso afirmativo, ¿Cuántas veces?:		Número desconocido	

DATOS TC

TC del tórax :	Yes	Fecha del TC de tórax:	14/01/1994 dd/mm/aaaa

TRATAMIENTO ACTUAL

Medicación para la enfermedad pulmonar:	Yes	Oxigenoterapia domiciliaria:	No

TRATAMIENTO SUSTITUTIVO

Alguna vez ha recibido tratamiento sustitutivo?	Yes	Fecha de inicio :	13/12/1992 dd/mm/aaaa
Dejó el tratamiento?	No	Fecha de interrupción:	dd/mm/aaaa

FUNCIONALISMO PULMONAR

Fecha de las primeras pruebas disponibles:	19/06/1986 dd/mm/aaaa			
FEV1 pre-broncodilatador (L):	1,3	litros	FEV1 post-broncodilatador (L):	1,4 litros
FVC pre-broncodilatador (L):	2,2	litros	FVC post-broncodilatador (L):	2,3 litros
VC lenta pre-broncodilatador (L):	2,2	litros	VC lenta post-broncodilatador (L):	2,3 litros
Fecha de las pruebas más recientes	14/12/2001 dd/mm/aaaa			
FEV1 pre-broncodilatador (L):	1,7		FEV1 post-broncodilatador :	1,9 litros
FVC pre-broncodilatador (L):	2,3		FVC post-broncodilatador :	2,3 litros
VC lenta pre-broncodilatador (L):	2,3	litros	VC lenta post-broncodilatador :	2,3 litros
KCO (%):		%		

ENZIMAS HEPÁTICAS

Enzimas hepáticas :	Yes	Fecha de determinación: dd/mm/aaaa	01/01/1999

ALAT/SGOT Elevada:	No
ASAT/SGPT Elevada:	No
GGT Elevada:	No
FA Elevada:	No

DATOS CUESTIONARIO ST GEORGE

Puntuación total SGRQ:

HISTORIA LABORAL

Trabaja actualmente:	Yes	Si **NO**, especifique el motivo:
Muestra de plasma?	Yes	
Muestra de sangre total?	Yes	

FECHA FINAL

Fecha de fallecimiento : dd/mm/aaaa

Causa de muerte :

Otra causa, especificar:

Se realizó autopsia:

Modificar Paciente - Cancelar

Patient N°: 206

PATIENT'S INITIALS: RAF

Country code: E **Inclusion date:** 04/02/2002

DEMOGRAPHICS

Date of birth:		Sex:	
12/04/1947 dd/mm/yyyy		Female	
Height	Height units	Weight (kg):	
149	Cm	57	kilos

SMOKING HABITS

Have you ever smoked?	No	Age started:	years old
Have you given up smoking?		Age stopped:	years old

Average daily consumption of cigarettes:

Average daily consumption of cigars:

Pipe - g/week:

REASON FOR DETERMINING AAT

Reason for determining AAT		Family screening	
Phenotype:	Z		
Other deficient phenotype:			
Date of diagnosis of AAT deficit:		18/07/1984	dd/mm/yyyy

CLINICAL HISTORY

Lung disease	Yes		
Chronic bronchitis	Yes		
Emphysema	Yes		
Asthma	Yes		
Bronchiectasis	Yes		
Other lung disease	No	Specify	
		Years old	
Age respiratory symptoms started		35	Months
Principal symptom	Attacks of dyspnoea		

Other diagnosis	Yes		
Diagnosis 1: rheumatic fibromyalgia			
ICD code			
Diagnosis 1	See Code Table	ICD version	
Diagnosis 2			
ICD Code			
Diagnosis 2	See Code Table	ICD version	
Diagnosis 3			
ICD Code			
Diagnosis 3	See Code Table	ICD version	
Lung transplant		Date of lung transplant:	dd/mm/yyyy
Reduction in lung volume		Date of reduction of lung volume:	dd/mm/yyyy
Liver transplant:		Date of liver transplant:	dd/mm/yyyy
Have you suffered from pneumonia?			
If so, how many times?		Unknown number	
TC data			
Thorax TC:	Yes	Date of Thorax TC:	14/01/1994 dd/mm/yyyy
CURRENT TREATMENT			
Medication for lung disease	Yes	Home oxygen therapy:	No
ALTERNATIVE TREATMENT			
Have you received an alternative treatment	Yes	Start date:	10/07/1995 dd/mm/yyyy
Did you stop treatment?	No	Interruption date	dd/mm/yyyy
PULMONARY FUNCTIONING			
Date of first tests available	19/06/1986	dd/mm/yyyy	
FEV1 pre-bronchodilator (L):	1.3 litres	FEV1 post-bronchodilator (L)	1.4 litres
FVC pre-bronchodilator (L):	2.2 litres	FVC post-bronchodilator (L)	2.3 litres
Slow VC pre-bronchodilator (L):	2.2 litres	Slow VC post-bronchodilator (L)	2.3 litres
Date of most recent tests	14/12/2001	dd/mm/yyyy	
FEV1 pre-bronchodilator (L):	1.7 litres	FEV1 post-bronchodilator (L)	1.9 litres
FVC pre-bronchodilator (L):	2.3 litres	FVC post-bronchodilator (L)	2.3 litres
Slow VC pre-bronchodilator (L):	2.3 litres	Slow VC post-bronchodilator (L)	2.3 litres
KCO (%):	%		
HEPATIC ENZYMES			
Hepatic enzymes: Yes		Date of determination: 01/01/1999 dd/mm/yyyy	

High ALAT/SGOT No

High ASAT/SGPT No

High GGT No

High FA No

ST GEORGE QUESTIONNAIRE DATA

Total score SGRQ:

WORK HISTORY

Do you currently work: Yes

If not, specify the reason

Plasma sample Yes

Total blood sample Yes

END DATE

Date of death: dd/mm/yyyy

Cause of death:

Other cause, specify:

Was an autopsy carried out:

ATTACHMENT F

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Ongoing research in Europe: Alpha One International Registry (AIR) objectives and development

R. A. Stockley[1], M. Luisetti[2], M. Miravitlles[3], E. Piitulainen[4], P. Fernandez[5] on behalf of the Alpha One International Registry (AIR) group

[1] Dept of Medicine, Queen Elizabeth Hospital, Edgbaston, Birmingham, and [5] Pharmanet, Buckingham Court, Kingsmead Business Park, High Wycombe, UK. [2] Clinica Malattie Apparto Respiraorio, IRCCS Policlinico San Mateo, Università di Pavia, Pavia, Italy. [3] Servei de Pneumologia, Institut Clínic del Tòrax (IDIBAPS), Hospital Clínic, Barcelona, Spain. [4] Dept of Respiratory Medicine, University Hospital, Malmö, Sweden.

CORRESPONDENCE: R. A. Stockley, Dept of Medicine, University Hospital Birmingham, Edgbaston, Birmingham, B15 2TH, UK. Fax: 44 1216978257. E-mail: r.a.stockley@bham.ac.uk

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ABSTRACT

In 1997, the World Health Organization recommended establishing an international registry of α1-antitrypsin deficiency. The objective of the present article is to describe the organisation of an international network of registries, the Alpha One International Registry (AIR), and the processes of enrolling and entering data.

By the end of 2005, the registry included individuals from 21 countries (from four continents). The inclusion criterion was either phenotypes PiZZ, PiSZ or other

severely deficient variants. Demographic and clinical information have been collected by a standardised questionnaire, translated for each country. Data are transferred to the AIR database at the Dept of Respiratory Medicine, University Hospital, Malmö, Sweden, either by e-mail or *via* two web-enabled questionnaires in HTML. All data are merged and checked for consistency and missing values.

Collection of data started in 1999 and, by September 2005, data on 2,150 individual patients (1,180 male) had been submitted. Of these, 1,855 (84%) have phenotype PiZ, 181 (8%) PiSZ and 114 (5%) other rare Pi phenotypes. The mean age at inclusion was 49.8 yrs (SD = 13.3) and the majority were index cases (64.1%).

The Alpha One International Registry is the largest specific α_1-antitrypsin deficiency registry, fulfilling a major World Health Organization recommendation. The success related to the convergence of national registries into a common database creating a unique registry beyond geographic boundaries and encompassing α_1-antitrypsin deficiency from various ethnic groups.

Although often regarded as a rare disorder, α_1-antitrypsin deficiency (α_1-ATD) is the most common of inherited deficiency states in the Western hemisphere, an apparent contradiction explained by widespread underdiagnosis. The condition was first identified in 1963 and is known to predispose to severe panlobular emphysema, cirrhosis, liver carcinoma and, less commonly, vasculitis and panniculitis 1. The present understanding of its genetic basis and the availability of simple screening and diagnostic tests offer a largely neglected opportunity to identify those with the deficiency who have developed severe pulmonary or hepatic disease. However, they also permit identification of deficient and undetected family members prior to the onset of disease, at a time when preventive measures can be most effective.

The major handicap to understanding and designing interventions is the relative infrequency (one in 1,600 to one in 2,000 in Europe) of the disorder, which has precluded the recruitment and study of sufficient patients for meaningful, adequately powered studies 2. In 1997, the World Health Organization (WHO) published state-of-the-art documentation 3 following a meeting of experts, and

identified questions that remained to be answered. A key recommendation was the establishment of national and international registries to enable data collection, collaborative research and, most specifically, a patient resource for the design and conduct of suitably powered clinical trials. This latter process required the novel design of collection methods for centralisation of data and an unprecedented international collaboration. The Alpha One International Registry (AIR) was initiated to comply with the WHO recommendation to establish an international registry of α_1-ATD, characterised in as standardised a way as possible by employing a common database. The main objectives of the registry were as follows: 1) to establish an international database of patients and their demographic details; 2) to promote basic and clinical research into α_1-ATD and to coordinate the activity; 3) to collect, assess and disseminate information concerning all aspects of α_1-ATD; and 4) to encourage support and awareness of α_1-ATD. The present article describes the methods and format of this unique database.

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METHOD

Organisation of the registry

AIR was founded in 1997 and included an initial group of European countries (the UK, Germany, Denmark, Sweden, the Netherlands, Italy, Spain and Switzerland), along with New Zealand, South Africa, Canada and a part of the USA. Other countries have since joined, including Denmark, Austria, Belgium, Australia, Poland, Finland, Latvia, Lithuania, Argentina and Brazil. By 2005, the registry included 21 countries from four continents.

The constituent parts of the registry are the general members, the council and the coordinating committee. Each national registry is represented on the council by one national delegate. This national delegate ensures the liaison between the national registry and AIR. The coordinating committee directs and conducts the general activities of AIR, and comprises a chairman, secretary, treasurer and two other members, all elected by the council.

AIR organises at least two annual administrative meetings, as well as a scientific meeting every 2 yrs to provide an update on research progress related to α_1-ATD [4].

Collection of data

All data in the registry are collected according to national and international rules of confidentiality of personal data and following approval by the corresponding Independent Review Boards. Confidentiality of the data is assured by coding the included patients with an identification number consisting of a six-digit field (four digits for the national registry number and two corresponding to each national telephone code).

The sole inclusion criterion for the registry is the presence of phenotype PiZZ, PiSZ or other severely deficient variants (serum α_1-antitrypsin (α_1-AT) concentrations <11 μM). From the beginning of the registry until 2005, only individuals aged >18 yrs were included, although from 2005 this age limit has been rescinded.

The questionnaire (available from the present authors by request) consists of standard demographic information (including age and sex), current and previous smoking history to calculate pack-yrs, a pulmonary history with the main symptoms, respiratory medication, the α_1-AT phenotype, reasons for α_1-ATD assessment, information on augmentation therapy, lung function (including pre- and post-bronchodilator spirometry, lung volumes and carbon monoxide gas transfer) and liver function tests (γ-glutamyl transferase, alanine transferase and aspartate transferase), comorbidities, whether the patient has undergone lung and/or liver transplantation and specific health-related quality of life measured by the St. George's Respiratory Questionnaire, social status and other diagnoses classified by the International Classification of Diseases code. The patients are followed up annually and information is collected to document

changes in characteristics of the disease, treatment, smoking habits and lung and liver function. The original English-language version of the questionnaire has been translated and adapted into the appropriate language for each country.

Transmission and validation of data

The database and data manager are located at the Dept of Respiratory Medicine, University Hospital, Malmö, Sweden. Data from the national registries are transferred periodically to the AIR database. Initially, the questionnaire was incorporated in a Microsoft Access sheet and each national delegate collected their own data and submitted it to the data manager by encrypted e-mail or by delivery of electronic media. All data were downloaded into a unique database and were checked by the national coordinator for consistency. The database manager then reviewed the data submitted and checked with the national coordinator if data was missing or calculated lung function appeared at variance. At the present time, data from Germany, Italy, Sweden and Canada are still periodically transferred to the central database using this process. Each national coordinator is able to review their own entries. An update of the data from all countries is presented at each AIR meeting and searched to answer specific queries raised by the council. The database cannot be accessed by a third party.

As early as 1999 it was recognised that some countries would experience great difficulty in centralising the collection of data in a single centre. Spain developed a web-enabled questionnaire in HTML, which was the interface for a database in Oracle, hosted at the web page of the National Society of Chest Physicians (SEPAR). By using a username and a password every physician in the country caring for an α_1-ATD individual was able to access the web page and complete the questionnaire online. The national delegate has a special user access and can check the quality of data whilst preserving the confidentiality. The Oracle database is adapted to the format text delimited as requested by the central data manager and submitted (encrypted) twice a year from 2001, to the central database in Malmö. The same web-enabled questionnaire in Spanish has been used from 2003 by the Argentinean registry, and the Portuguese translation has been used by the Brazilian registry from 2005.

Another web-enabled database was developed in the Netherlands in 2000, and is available in the UK, Switzerland, the USA, New Zealand, Australia, South Africa, Austria, Belgium and Poland. Data collected in these countries are submitted to the Netherlands and then periodically to the central database in Sweden.

All data downloaded to the central database are merged in a single database and checked for consistency and missing values by the data manager. Queries are sent to the national representatives for completion and resolution.

RESULTS

The number of patients for whom data has been submitted to the central database is shown in figure 1. Collection of data began in 1999 and by September 2005, data from 2,150 α_1-AT-deficient individuals (1,180 male, 968 female) had been submitted (in two subjects the sex was not reported). Of these subjects, 1,855 (84%) have phenotype PiZ, 181 (8%) phenotype PiSZ, and 114 (5%) have other rare Pi phenotypes with severe α_1-ATD. A total of 45 (2%) subjects have been excluded at present, as the Pi phenotype has yet to be reported, and 16 subjects have been excluded because of an inappropriate Pi phenotype (PiMZ, PiSS, *etc.*). Table 1 shows the number of subjects by country and the year when each country included its first patient (updated March 2006). The mean age of the subjects was 49.8 yrs (range 0–100 yrs; SD 13.3 yrs) at inclusion, although the age has yet to be submitted for 17 of the patients. The initial reasons for the α_1-AT analyses are shown in table 2. Table 3 compares the characteristics of patients in the AIR with those of patients in two large North American databases: the National Heart, Lung, and Blood Institute (NHLBI)

Registry and the Alpha One Foundation Research Network Registry (AOF-RNR).

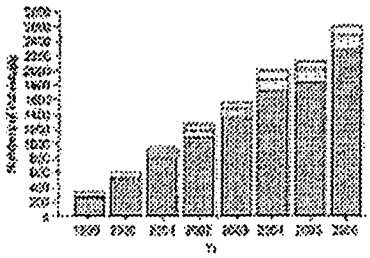

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Fig. 1— Cumulative increase of the Alpha One International Registry. By March 2006, a total of 2,627 α_1-antitrypsin (AT)-deficient individuals (2,285 PiZZ, 218 PiSZ, and 124 other rare α_1-AT-deficient phenotypes) were included in the register. □: Pi "other"; ▒: PiSZ, ╦: PiZZ.

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Table 1— The number of patients included in the Alpha One International Registry by country, last updated March 2006

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Table 2— The initial reasons for α_1-antitrypsin analysis

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Table 3— Characteristics of α_1-antitrypsin deficiency (α_1-ATD) subjects included in the Alpha One International Registry (AIR), the National Heart, Lung, and Blood Institute (NHLBI) registry, and the Alpha One Foundation Research Network Registry (AOF-RNR)

DISCUSSION

In the present paper, the successful implementation of a major recommendation made by the 1996 WHO workshop on α_1-ATD is described 3. Registries of individuals fulfilling careful diagnostic and assessment criteria, and enrolled on a national basis under the supervision of an expert database manager make available populations in whom understanding of this rare disease (*i.e.* disorders, such as α_1-AT, characterised by a prevalence of <5 out of 10,000 subjects) can be furthered. The success of AIR has been the convergence of national registries into a common database combining agreed information, thus creating a unique registry beyond geographical boundaries and encompassing α_1-ATD from varying ethnic groups. This is of particular relevance, since it has recently been shown that α_1-ATD is not confined to Northern European populations and their descendants alone but is a disorder with a worldwide distribution 5, 6. The development of a shared questionnaire, the adoption of a minimum requirement to ensure a quality control, and the electronic transfer of data, either by encrypted e-mail shipment of Access sheets or by a secure web-enabled database, greatly contributed to the success of AIR data validation, dissemination and rapid growth.

With 2,627 subjects enrolled (last updated March 2006; fig. 1•), AIR is the largest and most comprehensive registry for α_1-ATD (PiZ phenotype). Two other large registries for α_1-ATD exist; both are located in North America. The NHLBI Registry for individuals with severe α_1-ATD completed recruitment in 1996 and included 1,129 subjects, with the main goal of characterising the natural history of α_1-ATD, and with the rate of lung function decline and survival as major aims 7. The AOF-RNR is a separate registry; participating subjects have expressed a willingness to be approached for participation in studies, including randomised clinical trials 8. A board of physicians/investigators and patient advocates ensures data quality control; by 2001, the AOF-RNR included 1,204 individuals, although the phenotype is self-reported and hence contains unconfirmed PiZ patients. Besides differences concerning structure and enrolment mechanisms,

a major, intuitive difference between AIR and the two Northern American α_1-ATD registries is geography. AIR enrolees are mostly Europeans (1,745; 81% of the total included). Taking into account that 204 α_1-ATD subjects in the AIR are from the USA and Canada (and therefore they might be also present in both NHLBI and AOF registries), AIR includes a cohort of ≥90% α_1-ATD subjects that differs from that of the two Northern American registries. However; comparing some characteristics of the α_1-ATD series in AIR (current results) with the published ones in the NHLBI series 7 and in the AOF registry 8, there is a general concordance of basic characteristic data (table 3•). The disorder is usually diagnosed within the fifth decade of life and there is a slight preponderance of male subjects. The rate of ascertainment for family screening (more recently referred to as predispositional testing) 9 is similar between AIR and the NHLBI registry (19.2 and 19.8%, respectively). The main difference between the two registries is the distribution of α_1-ATD phenotypes. AIR included a lower percentage of PI*Z subjects than the NHLBI registry (86.2 *versus* 97.3%, respectively). Furthermore, the PI*SZ and rare genotypes are eight- and three-fold higher in AIR, respectively. This might reflect the different epidemiology of S and rare α_1-ATD variants in the European countries 2, 5, 6, 10, 11 or different inclusion criteria. Comparison with the AOF-RNR is, however, uncertain with reference to phenotype, since the AOF-RNR registry includes mainly self-reported deficiency patients and includes intermediate (PI*MZ) and undetermined phenotypes, whereas those in AIR are confirmed. Finally, the smoking habit is similar among all three registries, although the lower rate of active smoking in the AOF-RNR may reflect the higher rate of awareness about smoking cessation in the self-reported patients. Detailed analysis of these and other characteristics of the α_1-ATD subjects in AIR will be the subject of future publications.

There are some features of the AIR development that exceed those of a simple registry for a rare disease. First, AIR has facilitated collaboration between clinicians from 21 different countries in four continents, 18 of which have already entered patients to the registry (table 1•). Existing national registries for α_1-ATD, such as those in Sweden, the UK, Spain 12 and the Netherlands, joined other registries, such as that in Italy, that were established to join the AIR on its

formation. More recently, registries have joined as they have been formed in response to the AIR. Thus, AIR has played a central role in raising awareness of α_1-ATD in countries with medium-to-low prevalence of the disorder. Secondly, AIR and its scientific initiatives, such as the international conferences 4, have not only gathered clinicians concerned with α_1-ATD but have also encouraged a number of scientists, including geneticists, epidemiologists, biochemists and pathologists, as well as representatives of patient support groups, public health and pharmaceutical companies, to collaborate with a common goal. It is clear that such synergy is critical for significant advances in and a better understanding of α_1-ATD, its pathogenesis, its current management and the development of novel therapeutic strategies, with a patient database needed to successfully deliver clinical trials (in this uncommon condition). In this respect, two such trials are currently underway: EXACTLIE (Exacerbations and Computer Tomography in Laurell's syndrome as Investigative Endpoints), which is a 2-yr, placebo-controlled intravenous augmentation study and REPAIR (Retinoids for Emphysema Patients and Alpha-1-antitrypsin International Registry), a 12-month trial of a retinoic acid receptor-γ agonist. In addition, the consortium has been successful in obtaining two European Union grants (AIR genetics and SPREAD (grant number RNDV07773). Finally, data gathered *via* AIR and, in particular, in the UK and Canadian registries has led to a new study confirming a beneficial effect of augmentation therapy for emphysema arising from α_1-ATD and to a meta-analysis of this and published studies of α_1-ATD 13, 14.

In conclusion, a major international collaboration is described herein that has provided a common database to advance in understanding and treatment of α_1-antitrypsin deficiency.

APPENDIX: ALPHA ONE INTERNATIONAL REGISTRY (AIR) GROUP

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Structure of AIR

AIR Chairman: J. Stolk (the Netherlands).

Past chairmen: N. Konietzko (Germany) and R.A. Stockley (UK).

Council: M. Luisetti (Italy), M. Miravitlles (Spain), E. Piitulainen (Sweden), P. Fernandez (UK), K.R. Chapman (Canada), A. Dirksen (Denmark), J. Houtsebaut (Belgium), J. Jardim (Brazil), G. Menga (Argentina), C. Vogelmeier (Germany), J. Zielinski (Poland), G. Ainslie (South Africa), E.W. Russi (Switzerland), E. Campbell (USA), M. Epton (New Zealand), K. Schmid (Austria), A. Krams (Latvia), M. Zolubas (Lithuania), S. Saarelainen (Finland) and J. Burdon (Australia).

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